does not substantially enhance endotoxin shock, the mutant is not lethal, or the mutant is nonlethal but retains mitogenicity comparable to that of the wild type SPE-A toxin.

26. (New) A vaccine for protecting animals against at least one biological activity of wild-type SPE-A comprising: an effective amount of at least one mutant SPE-A toxin according to claim 19.

27. (New) A pharmaceutical composition comprising: a mutant SPE-A according to claim 19 in admixture with a physiologically acceptable carrier.

28. (New) A method for protecting an animal against at least one biological activity of a wild type SPE-A comprising: administering a vaccine according to claim 26 to an animal.

29. (New) A method for reducing symptoms associated with toxic shock comprising: administering a vaccine according to claim 26 to an animal.

REMARKS

Applicants have received and reviewed the Office Action dated January 18, 2000. By way of response, Applicants have cancelled claims 2, 10, 11, 15 and 16 without prejudice, amended claims 1 and 3-9, and added claims 19-29. Claims 1, 3-9, 12-14 and 17-29 are pending. No new matter is introduced. Applicants submit that the amended and newly presented claims are supported by the specification.

In particular, support for the recitation in the claims regarding residues leucine-41 and leucine-42 and regarding domain B beta strand comprising residues 41 through 47 of SPE-A can be found in the specification at least at page 18, lines 16-26.

For the reasons given below, Applicants respectfully submit the amended and newly presented claims are in condition for allowance, and notification to that effect is earnestly solicited.

Petition for Extension of Time

It is noted that a three-month petition for extension of time is necessary to provide for timeliness of the response. A request for such an extension is made extending the time for response from April 18, 2000 to July 18, 2000.

Election/Restriction

Applicants note the Examiner's acknowledgement of the unelected claims. Applicants have cancelled the unelected claims, claims 15 and 16, without prejudice.

Nucleotide and/or Amino Acid Sequence Disclosures

Applicants have provided herewith a computer readable form copy of the Sequence Listing and the accompanying statement that the paper and computer readable copies are the same. The specification has also been amended at page 54, line 24, to insert a SEQ ID NO for the sequence found there.

Accordingly, it is believed that the application complies with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures, and notification to that effect is earnestly solicited.

Rejection of Claims Under § 112, Second Paragraph

The Examiner rejected claims 1-14, and 17 -18 under 35 U.S.C. § 112, second paragraph. The Examiner objected to certain terms and phrases employed in the claims. Applicants respectfully traverse this rejection.

In particular, the Examiner objects to the use of the phrases "mutant SPE-A toxin", "fragment thereof", and "wild type SPE-A toxin".

The phrase "fragment thereof" is not employed in the amended and newly presented claims.

With regard to the other phrases objected to, Applicants respectfully direct the Examiner's attention to the specification as filed. The term "mutant SPE-A toxin", and its characteristics are discussed and defined at least at page 9, line 16-29. The term "wild type SPE-A toxin", its characteristics, biological activity, etc. is discussed and defined at least at page 8,

line 8 through page 9, line 4. The specific protein sequences related to these terms can be found in the sequence of Figure 3 as well as the attached sequence listing. The amino acid number designations are made by reference to this sequence. Applicants submit that these definitions and descriptions given in the specification allow one of ordinary skill in the art to be reasonably apprised of the metes and bounds of the claimed subject matter. The protein sequence that is provided adds further clarity to the definition of these terms. Therefore, Applicants respectfully submit that the terms "mutant SPE-A toxin" and "wild type SPE-A toxin" are clearly defined by the specification.

The Examiner's logic suggests that every claim relating to a protein or peptide must include the sequence of that protein or peptide. Applicants are unaware of any authority that requires such cumbersome claiming. Claims commonly employ nouns to refer to elements of an apparatus, composition, chemical, nucleic acid, or protein, and describe or define these nouns in the specification. If the Examiner can provide some authority in support of the Examiner's desire to have the entire sequence of the protein in the claim, Applicants will consider providing such cumbersome claims.

The Examiner also objects to the recitation of the substitution positions through use of the phrase "in N-terminal alpha helix 3... or is a cysteine", in claim 2, and the use of numbered amino acids in claims 3-11. Applicants respectfully direct the Examiner's attention to the specification at least at page 46, line 10. The specification describes the phrases used in claim 2 for describing the regions of the mutant SPE-A toxin by the amino acid positions that make them up. The numbered amino acids that comprise those regions as well as the numbered amino acid positions utilized in claims 3-11 can be determined by reference to the amino acid sequence provided in the application. Applicants respectfully submit that the phrase "in N-terminal alpha helix 3..." and the numbered amino acids are clearly defined by the specification.

The Examiner objects to the recitation of the phrases "substantially nonlethal", "substantially corresponding", "substantially enhance", and "comparable to" in claims 1 and 12. Applicants respectfully direct the Examiner's attention to the specification as filed. The term "substantially nonlethal" is described and defined at least at page 12, lines 14-16. This passage describes that the claimed mutant SPE-A toxins are substantially nonlethal in rabbits when administered by miniosomotic pump (as described in Example 2) at the same or greater dose than

a wild type SPE-A toxin. Specifically, the mutant SPE-A is substantially nonlethal if when administered to a rabbit at the same dose as the wild type toxin, less than about 10-20% of rabbits die. Id. Applicants respectfully submit that the phrase "substantially nonlethal" is clearly defined by the specification.

The Examiner also objected to the term "substantially corresponding" in claim 1. Applicants respectfully direct the Examiner's attention to the specification at least at page 9, lines 5-15. This passage describes the characteristics of proteins that "substantially correspond" to wild type SPE-A toxin. Applicants respectfully submit that the phrase "substantially correspond" in claims 1 and 12 is clearly defined by the specification.

The Examiner further objected to "substantially enhance" in claim 12. Applicants respectfully direct the Examiner's attention to the specification at least at page 13, lines 29 through page 14, line 2. This passage describes that a lack of enhancement of endotoxin shock can be evaluated in rabbits as described in Example 4. Substantially no enhancement of endotoxin shock is seen when less than about 25% of the animals develop shock when the mutant SPE-A toxin is co-administered with endotoxin as compared to wild type SPE-C activity at the same dose. Preferably, substantially no enhancement of endotoxin shock results in none of the animals developing shock. Id. Therefore, Applicants respectfully submit that the phrase does not "substantially enhance" endotoxin shock is well defined in the specification as filed.

The Examiner objected to the phrase "comparable to" in claim 12. Applicants respectfully direct the Examiner's attention to the specification at least at page 15, line 27-32. This passage describes the enumeration in claim 12 of "nonlethal but retains mitogenicity comparable to that of the wild type SPE-A toxin." The specification even gives an example of a mutant that has mitogenicity comparable to the wild type SPE-A toxin. Page 15, line 31-32. Applicants respectfully submit that the phrase "comparable to" is well defined in the specification as filed.

Accordingly, it is believed that the amended and newly presented claims fully comply with § 112, second paragraph, withdrawal of this rejection is respectfully requested.

Rejecti n of Claims Under § 112, First Paragraph

The Examiner rejected claims 1-4, 6, 8, 10, 12-14, and 17-18 under 35 U.S.C. §112, first paragraph. The Examiner asserts that the specification does not enable the full scope of the claimed mutants of SPE-A. Applicants respectfully traverse this rejection.

The Amended and Newly Presented Claims

Applicants note that the amended and newly presented claims relate to mutants of SPE-A including substitutions at particular amino acids or in particular structural domains. Each of these residues and structural domains are specifically called out in the present specification as preferred locations for substitutions. For example, support for the recitation in the claims regarding residues leucine-41 and leucine-42 and regarding domain B beta strand comprising residues 41 through 47 of SPE-A can be found in the specification at least at page 18, lines 16-26. The amended and newly presented claims also recite substitution at residues that the examiner has acknowledged are enabled by the specification. In certain claims, these residues are described by the secondary structural feature in which they reside. As described below, these various residues and structural features are well supported by the specification has filed and substitutions at these sites are enabled.

Applicants are looking forward to the Examiner's acknowledgment that the amended and newly presented claims are enabled and comply with section 112 first paragraph, and that they are allowable.

Detailed Response to the Examiner's Rejection

Applicants appreciate the Examiner's acknowledgment that the specification is enabling for single, double, and triple mutants of SPE-A toxin N20D, C87S, K157E, S195A, K16N, D45N, N20D/C98S, N20D/K157E, and N20D/D45N/C98S; as well as for the method of protecting an animal or reducing symptoms administering the mutants.

The Examiner goes on to note that the claims include any SPE-A mutant toxin or any mutant combination up to six point mutations in a single toxin protein, but that the specification fails to provide guidance as to any other amino acid substitution in SPE-A toxin or any other toxin. The present application does, however, specifically teach that the relevant portion of SPE-

A includes only 220 amino acids. From this rather small protein, the specification teaches 41 specific amino acid residues that are preferred sites for mutations. The present specification also discloses 5 secondary structural features of SPE-A that are preferred regions in which amino acids can be mutated. The 5 secondary structural features include 2 beta strands, 2 helices, and a disulfide bonding region. (specification including at page 46, line 15-17, and page 16, line 3-8). By describing these numerous discrete residues and specific structural features of the protein that are suitable for making mutations that yield a substantially nonlethal SPE-A, Applicants have met several descriptions of the standard for enablement under § 112, first paragraph.

The Standard for Enablement as Stated by the Federal Circuit and Described in the MPEP

The MPEP provides one statement of the standard for enablement at § 2164.08, which reads:

> Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).
>
> As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).
> ...
>
> How a teaching is set forth, by specific example or broad terminology, is not important. In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). ... In In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:
>
> > [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.
>
> M.P.E.P. at 2164.08.

The MPEP describes that claims must have a reasonable correlation with the specification, must be commensurate in scope with the specification, can be provided either by specific examples or

broad terminology, and cannot be limited to the preferred or exemplified embodiments. Applying this standard leads to the conclusion that the presently pending claims are enabled.

The Present Claims are Enabled According to The Standard of the MPEP and Federal Circuit

The MPEP indicates that "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." In this case, the claims relate to a mutant SPE-A toxin that is substantially nonlethal. The entire mature protein consists of only 220 amino acids. The specification specifically recites 5 secondary structural features of this relatively small protein that are suitable locations for mutations yielding a nonlethal protein. Further, the specification explicitly calls out 41 amino acid residues of this relatively small protein that are suitable sites for mutation. This detailed disclosure of features and residues that can be mutated in SPE-A reasonably correlates with the scope of the present claims. Therefore, Applicants are entitled to a claim that broadly describes a nonlethal SPE-A mutant and includes each of these 5 secondary structural features and 41 amino acid residues. This is the subject matter of the amended and newly presented claims. Thus, the present disclosure meets the standard for enablement as described in the MPEP at § 2164.08 and in In re Fisher.

The MPEP further states that the only relevant concern is whether the disclosure provides a scope of enablement commensurate with the scope of the claims. Again, the present disclosure specifically recites 5 secondary structural features and explicitly calls out 41 residues of a relatively small protein as sites that are suitable for mutation. This extensive description of suitable regions of the protein is disclosure commensurate with the scope of claims to mutations throughout the protein. Therefore, Applicants are entitled to a claim that broadly describes a nonlethal SPE-A mutant and includes each of these 5 secondary structural features and 41 amino acid residues. The presently pending claims are such claims. Thus, the present disclosure is enabling according to the standard expressed in the MPEP at 2164.08 and in In re Moore supra.

The MPEP notes that an enabling disclosure can include either specific example or broad terminology. The present application includes working examples demonstrating the production of specific nonlethal SPE-A mutants, provides specific description of 5 secondary structural features that are suitable sites for mutations, and explicitly calls out 41 amino acids preferred as residues to be mutated. Therefore, Applicants are entitled to a claim that broadly describes a

nonlethal SPE-A mutant and includes each of these 5 secondary structural features and 41 amino acid residues. The presently pending claims are such claims. Thus, the present disclosure meets the standard for enablement as described in the MPEP at 2164.08 and in re Marzocchi.

The MPEP also notes that limiting an inventor to claims to preferred materials or what the inventor has found will work does not serve the constitutional purpose of promoting progress in the useful arts. In the present case, Applicants have exemplified several nonlethal mutants of SPE-A, have explicitly described 41 amino acids that are preferred sites for making such mutants, and specifically describe 5 secondary structural features that are suitable locations for mutations eliminating toxicity. By the standard expressed in In re Goffe and in the MPEP at 2164.08, constitutional purposes would be defeated by limiting the inventor to the specifically disclosed mutants of SPE-A. Thus, the inventors are entitled to a generic claim including all of these nonlethal mutants of SPE-A.

The MPEP then continues in § 2164.08 with examples from court cases applying the enablement standard to biotechnological inventions. The MPEP discusses the Amgen case in which Amgen claimed many DNA sequences encoding analogs of a protein, but told how to make and use only a very few of them. The claims of the present application cover only a finite number of nonlethal mutants of SPE-A; and the present specification specifically describes 5 secondary structural features of the protein that are suitable locations for these mutations and explicitly calls out 41 amino acids that are preferred residues for mutation. The present application tells how to make and use a wide variety of mutants and enables a broad claim including all of these mutants. This presents another example of how the present application meets the standard for enablement as expressed in the MPEP at 2164.08. A similar analysis applies to show enablement in the present application compared to the other specific examples of biotechnological inventions described in the MPEP at 6164.08. Therefore, Applicants are entitled to a claim that broadly describes a nonlethal SPE-A mutant and includes each of these 5 secondary structural features and 41 amino acid residues. The presently pending claims are such claims.

Applicants' specification need not specifically describe how to obtain each and every nonlethal mutant of SPE-A. Applicants' invention is enabled even if it requires some experimentation to make some of the nonlethal SPE-A mutants. The necessity of some

experimentation does not preclude enablement under § 112, the key is whether the experimentation is undue. In re Angstadt at 218-219. Even a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides reasonable guidance with respect to the direction the experimentation should proceed. Ex parte Jackson, 217 USPQ 804, 807 (Bd. App. 1982).

Applicants provide more than reasonable guidance regarding the direction in which experimentation should proceed. For example, Applicants provide a lengthy and specific description of structural features and amino acid residues that are suitable sites for mutations in SPE-A (specification including at page 46, line 15-17, and page 16, line 3-8). The most preferred amino acid substitutions are described in the specification at least at page 25, lines 13-27 and in claims 3 through 11. Although methods for producing mutant proteins are well known to those of skill in the art, methods for making mutants are disclosed in the specification at least at page 12, lines 1-8; and in Examples 3 and 5 at pages 46 and 53 respectively. Well known and routine methods for determining the nonlethal nature of a SPE-A mutant are described in the specification at least at page 12, line 9-20, and in Example 4, and 6. The specification provides the key information of the features and residues on SPE-A that can provide nonlethal mutants. Those mutants can be made and evaluated by methods that are routine and that are described in the patent application. The fact that mutants would have to be made and assayed for lethality to determine whether a given SPE-A mutant is within the scope of the claims does not constitute "undue experimentation", particularly in an art where the level of skill is so high. In re Wands, 858 F2d 731 at 739 (Fed. Cir. 1988). Therefore, according to the standards of In re Angstadt, Ex parte Jackson, and In re Wands, the present claims are enabled.

Not only does the present application specifically identify particular regions and residues of SPE-A that are suitable for mutation, it provides working examples detailing success in producing several nonlethal SPE-A mutants. The examples describe 9 SPE-A mutants that were made and evaluated. Four of the nine were tested for lethality, and two were determined to be nonlethal.

Thus, Applicants have met several different standards for demonstrating that the claimed mutants are enabled. First, the fact that Applicants have made nonlethal mutants indicates that the specification enables a broad claim reciting nonlethal mutants. Second, Applicants'

specification meets standards of enablement established by the Patent Office and the Federal Courts. Therefore, Applicants' disclosure of numerous specific regions and residues suitable for making nonlethal SPE-A mutants provides enabling basis for a claim including all of these mutants, such as claims 1-14, 17, and 18.

Conclusion

In conclusion, based on the above, Applicants respectfully submit that the claims are fully enabled by the specification as filed. Applicants respectfully request withdrawal of this rejection.

Rejections Under § 102(b)

The Examiner rejected claims 1-2, 12-14, and 17-18 under 35 U.S.C. § 102(b) as being anticipated by *Hartwig et al.* (International Immunology 5 (8):869-875, (1993)). Applicants respectfully traverse this rejection.

Hartwig et al. does not disclose, nor does it discuss, the important characteristic of non-lethality. Further, this reference does not disclose or suggest the particular residues and structural features recited in the amended and newly presented claims. Therefore, *Hartwig et al.* does not disclose every element of the invention, and does not suggest them, so it cannot anticipate or make obvious the claimed invention.

Accordingly, based on the foregoing differences, it is respectfully submitted that the *Hartwig et al.* reference does not teach the presently claimed invention, and withdrawal of this rejection is respectfully requested.

The Examiner also rejected claims 1-2, and 12-14 under 35 U.S.C. § 102(b) as being anticipated by *Kaller et al.* (J. Exp. Med. 175:387 (1992)). Applicants respectfully traverse this rejection.

Kaller et al. discloses mutants of staphylococcal enterotoxin B. Staphylococcal enterotoxin B is not the same toxin as SPE-A. Therefore, *Kaller et al.* does not anticipate the present invention.

Accordingly, based on the foregoing differences, it is respectfully submitted that the *Kaller et al.* reference applied by the Examiner does not teach the presently claimed invention, and withdrawal of this rejection is respectfully requested.

The Examiner rejected claims 1-3, 6, 8, 12-14, and 17-18 under 35 U.S.C. § 102(b) as being anticipated by *Okonogi et al.* (U.S. Patent No. 4,172,126). Applicants respectfully traverse this rejection.

Okonogi et al. discloses a method for inactivating microbial toxins via the addition of tannins. The addition of tannins to proteins forms insoluble protein tannates. The tannin treated microbial toxins of *Okonogi et al.* would be insoluble protein-tannin complexes. These are not mutants of SPE-A. Therefore, *Okonogi et al.* does not anticipate or make obvious the present invention.

Accordingly, based on the foregoing differences, it is respectfully submitted that the *Okonogi et al.* reference applied by the Examiner does not teach the presently claimed invention, and withdrawal of this rejection is respectfully requested.

The Examiner also rejected claims 1-6, 8-10, and 12-14 under 35 U.S.C. § 102(b) as being anticipated by *Kline et al.* (Infection and Immunity 64(3): 861-869 (1996)). First, the *Kline et al.* reference is not properly considered as prior art against the present application. The *Kline* reference was published in March of 1996, which is less than one year before the priority date of the present application, December 6, 1996. If the Examiner maintains this rejection with respect to the amended and newly presented claims, Applicants will, if appropriate, submit a Declaration Under 37 C.F.R. § 1.131 by Dr. Patrick Schlievert stating that the presently claimed invention was developed before the publication date of the *Kline et al.* reference.

Provisional Double Patenting Rejection of Claims

The Examiner rejected claims 1-14, and 17-18 under statutory type and/or obviousness-type double patenting as being unpatentable over the copending Application No. 08/973,391. Applicants will address this rejection when it becomes absolute, at which time a terminal disclaimer will be made, if appropriate.

Summary

In summary, each of claims 1, 3-9, 12-14 and 17-29 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below, if the Examiner believes that doing so will expedite prosecution of this patent application.

Respectfully submitted,

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